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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,826	01/05/2004	Cecile Casterman	04958.0008-08000	4193

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,826	CASTERMAN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/5/04, 6/28/04, 1/23/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-63* is/are pending in the application.

4a) Of the above claim(s) *23,24,28-30,34,36-50 and 55-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,25-27,31-33,35 and 51-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. 08/471,284.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/15/04, 7/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 1/5/04 and 6/28/04 and Applicant's response filed 1/23/06 are acknowledged and have been entered.

2. Applicant is required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings for Figure 7 and Tables 1-5 on pages 52-56). See 37 C.F.R. 1.821(d)

It is noted by the Examiner that Applicant has provided direction on page 8 of Applicant's amendment filed 6/28/04 to replace Tables 1-5 at pages 51-55 [52-56] of the instant specification with replacement pages; however, no replacement pages for said Tables are of record in the said amendment.

3. New corrected drawing(s) in compliance with 37 CFR 1.121(d) is/are required in this application because the copy of Figure 7A submitted contains handwritten changes.

It is noted by the Examiner that Applicant has requested on page 9 of the amendment filed 6/28/04 that the Figure 7A be amended to include SEQ ID NO along side of each sequence listed in that figure, as indicated on the attached copy of the originally filed drawing (said copy not marked amended).

Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

4. Applicant's election of Group I (claims 18-36 and 51-59), and species of fragment of an immunoglobulin which is the variable region of a heavy chain, said variable region devoid of normal light chain interaction sites, and Applicant's election with traverse of the species of "labeled with a detectable label" that is "a radioactive label" in Applicant's response filed 1/23/06 is acknowledged.

With regard to Applicant's election of Group I and species of Ig VH, because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

With regard to Applicant's traversal of the species requirement, the basis for the traversal is that the label is not an essential feature of the claims.

Applicant's argument has been fully considered, but is not persuasive.

It is the Examiner's position that the requirement for species election is not contingent upon the label being an essential feature of the claims. Applicant is reminded that if the elected species is not found upon a search of the prior art, the search will be extended to another species.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-21, 25-27, 31-33, 35 and 51-54 read upon the elected species.

Upon consideration of the prior art, the search has been extended to include the species of "immunoglobulin or a fragment thereof according to claim 19, which has a constant region which is devoid of CH1 domain."

Accordingly, claims 23, 24, 28-30, 34, 36 and 55-59 (non-elected species of Group I) and claims 37-50 and 60-63 (non-elected groups II-XII) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 18-22, 25-27, 31-33, 35 and 51-54 are currently being examined.

5. The reference crossed out in the Form 1449 filed 7/1/04 has not been considered because the publication date has not been provided. It will be considered in the next Office Action if Applicant will provide said publication date.

6. The application is objected to because of alterations which have not been initialed and dated as is required by 37 CFR 1.52(c). The handwritten alterations, *i.e.*, markings, appear on pages 14, 17, 35, 38, 39 and Tables 3-5.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware of in the specification.

8. The disclosure is objected to because of the following informalities:

a. There is a large space on page 33 of the instant specification.

b. The use of the trademarks SEPHAROSE and SEPHADEX have been noted on page 50 at lines 10 and 15, respectively, in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.
Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

c. The symbol following "Bluescript" on page 22 at line 5 of the third full paragraph should be contiguous with the word "Bluescript."

d. Figure 7 in the Brief Description of the Drawings (listed as "Figures" by Applicant) should disclose "SEQ ID NO: 92-108," not "SEQ ID NO: 108."

Appropriate correction(s) is/are required.

9. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

10. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 18-22, 25-27, 31-33, 35 and 51-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the specification and claims as originally filed is as follows: an immunoglobulin or fragment thereof that specifically binds an antigen of interest, and wherein the said immunoglobulin or said fragment thereof comprises a variable region of a heavy polypeptide chain being devoid of normal light chain interaction sites. Applicant points to support for the claims in the amendment filed 6/28/04 on pages 17-18. However, the originally filed disclosure is to an immunoglobulin comprising two heavy polypeptide chains sufficient for the formation of at least one complete antigen binding site, wherein the immunoglobulin is devoid of light polypeptide chains.

13. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application, *i.e.,* 1/5/04, due to the presence of new matter in the claims as enunciated supra at item #12 of this action.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Ungar-Waron *et al* (Isr. J. Vet. Med. 1987, Vol. 43(3), pages 198-203, IDS reference) as evidenced by Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference) and as evidenced by EP 0739981 A1 and Roux *et al* (PNAS USA 1998, Vol. 95, pages 11804-11809, IDS reference).

Ungar-Waron *et al* teach a 40 Kd IgG from Camelid serum and composition thereof. Ungar-Waron *et al* teach that when camel serum was precipitated using ammonium sulfate, separated by DEAE-Sephacel, ultrafiltration and analyzed by IEP, two bands of 155 Kd and 100 Kd were visualized under non-reducing conditions, the 100Kd band dissociating into the 40 Kd band upon reducing conditions (especially Results and Discussion sections).

Evidentiary reference Hamers-Casterman *et al* teach VHH (V for variable region of heavy chain) from *Camelid* (infected with trypanosomes) serum that bind a large number of antigens present in a ^{35}S methionine-labeled trypanosome lysate, said VHH consisting of heavy-chain VHH dimers devoid of light chains and lacking the CH1 domain that binds to the light chain. Hamers-Casterman *et al* teach that the two 100 Kd immunoglobulin fractions upon reduction yield only heavy chains of 46 Kd and 43 Kd (see entire article, and especially second paragraph of article).

Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers (especially page 11804, column 2, paragraph before Materials and Methods section).

Although the art reference does not teach that the 40 Kd IgG band from *Camelid* serum contains VHH lacking CH1 and devoid of light chains or binds antigens such as those recited in instant claim 53, since evidentiary reference Hamers-Casterman *et al* teach the approximately 40 Kd size of the VHH lacking CH1 and devoid of light chains in *Camelid* serum upon reduction of the 100 Kd IgG that bind antigens in a lysate containing proteins, carbohydrates and nucleic acids from an infectious agent and that some *Camelids* have high anti-trypanosome titers and Roux *et al* teach that in *Camelids*, two of their three IgG subclasses contain no light chains and the unassociated VH domains interact with antigen as monomers, therefore the claimed antibody appears to be the same or similar to the antibody of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Evidentiary reference EP 0739981 A1 teaches that the superior solubility of Camelid VH domain along with its small size and amino acid sequence of the framework region that is very homologous to that of human, ensure a minimum of immunogenicity when administered to humans (especially page 11 at lines 14-23), *i.e.,* that it is "suitable for use in *in vivo* diagnosis."

However, claims 31 and 32 are also included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims, absent a structural difference in the product, *i.e.,* potential differences in glycosylation of the product depending upon the presence of potential glycosylation sites in the primary structure of the product as produced either in a eukaryotic cell or in a prokaryotic cell; in addition, the art reference teaches the IgG antibodies are made by eukaryotic cells, *i.e.,* are made by B cells in *Camelids*, and therefore the claimed antibody appears to be the same or similar to the antibody of the prior art absent a showing of unobvious differences.

Claims 51 and 52 are included in this rejection because the art reference teaches partially purified and substantially purified fractions containing of IgG from *Camelid* sera, *i.e.,* a "composition comprising an Immunoglobulin or fragment thereof..."

16. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Prelli and Blas (J. Immunol. 2/1/92, Vol. 148(3), pages 949-952, IDS reference) as evidenced by Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference).

Prelli and Blas teach a monoclonal Ig H (heavy chain) not associated with Ig light chain in human serum or urine, that these have a normal V region amino terminal sequence followed by an internal deletion of the remaining V and the entire CH1 domains, the latter of which includes the cysteine residue that bridges the heavy to light chain and the first constant intrachain bond, with sequencing commencing at the hinge region (especially abstract, introduction and discussion). Prelli and Blas further teach various stages in purification of the Ig H (especially materials and methods). Prelli and Blas teach radioalkylation of the monoclonal Ig H (especially materials and methods on page 949 at column 2, paragraph 3 on page 949). Prelli and Blas teach isolating the Ig H and labeling it with a radioactive label (especially materials and methods, paragraphs 1 and 2).

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Claims 31 and 32 are included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or "suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

Claims 33 and 35 are included because the art reference teaches labeling the protein.

Claims 51 and 52 are included in this rejection because the art reference teaches compositions comprising the Ig H such as in purification of the protein and in reduction and radioalkylation *i.e.,* a "composition comprising an Immunoglobulin or fragment thereof..."

Evidentiary reference Hamers-Casterman *et al* teach VHH (V for variable region of heavy chain) from *Camelid* (infected with trypanosomes) serum that bind a large number of antigens present in a ^{35}S methionine-labeled trypanosome lysate, said VHH consisting of heavy-chain VHH dimers devoid of light chains and lacking the CH1 domain that binds to the light chain (see entire article).

Although the art reference does not teach that the monoclonal Ig H binds antigens such as those recited in instant claim 53, the art reference teaches that the Ig H V region is of normal length and evidentiary reference Hamers-Casterman *et al* teach that VHH antibodies from *Camelids*, said VHH antibodies also lacking a CH1 region, are capable of binding antigens; therefore the claimed antibody appears to be the same or similar to the antibody of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition

of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the antibody of the instant invention and that of the prior art. See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

17. Claims 18-22, 25-27, 31-33, 35 and 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference) and as evidenced by EP 0739981 A1.

Hamers-Casterman *et al* teach VHH (V for variable region of heavy chain) from *Camelid* (infected with trypanosomes) serum that bind a large number of antigens present in a ^{35}S methionine-labeled trypanosome lysate, said VHH consisting of heavy-chain VHH dimers devoid of light chains and lacking the CH1 domain that binds to the light chain (see entire article).

Claims 25-27 are included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Claims 31 and 32 are included in this rejection because the intended uses of the immunoglobulin "suitable for use in *in vitro* diagnosis" or suitable for use in *in vivo* diagnosis", respectively, do not carry patentable weight per se.

In addition, evidentiary reference EP 0739981 A1 teaches that the superior solubility of Camelid VH domain along with its small size and amino acid sequence of the framework region that is very homologous to that of human, ensure a minimum of immunogenicity when administered to humans (especially page 11 at lines 14-23), *i.e.,* that it is "suitable for use in *in vivo* diagnosis."

Claims 33 and 35 are included in this rejection because the art reference teaches labeling the VHH with a ^{35}S methionine-labeled trypanosome lysate, thus meeting the claim limitation "labeled with a detectable label" that is "a radioisotope", respectively, by indirectly labeling the VHH.

Claims 51 and 52 are included in this rejection because the art reference teaches purified fractions containing VHH in the IgG_1, IgG_2 and IgG_3 fractions of *Camelid* sera, *i.e.,* a "composition comprising an Immunoglobulin or fragment thereof..."

Although the art reference does not teach that the VHH bind a protein, carbohydrate or nucleic acid, since the art reference does teach a lysate comprising all three components of trypanasoma, therefore the claimed antibody appears to be the same or similar to the antibody of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the antibody of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 18-22, 25-27, 31-33, 35 and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamers-Casterman *et al* (Nature 3 June 1993, Vol. 363, pages 446-448, IDS reference) in view of Schlom (Mol. Cell. Res. Fut. Diagn. Ther. 1990, pages 95-133).

Hamers-Casterman *et al* teach VHH (V for variable region of heavy chain) from *Camelid* (infected with trypanosomes) serum that bind a large number of antigens present in a ^{35}S methionine-labeled trypanosome lysate, said VHH consisting of heavy-chain VHH dimers devoid of light chains and lacking the CH1 domain that binds to the light chain. Hamers-Casterman *et al* teach that the VHH antibodies could be an invaluable asset in the engineering of soluble VH domains for diagnostic, therapeutic and biochemical purposes since they have undergone affinity maturation (*i.e.,* "the selective refinement in the specificity and affinity that accompanies B–cell maturation". (see entire article).

Hamers-Casterman *et al* does not teach a VHH that specifically binds a protein present on tumor cells.

Schlom teaches that there are several types of tumor-associated antigens (TAA) that may act as targets for mAb-based diagnostics and therapeutics (especially page 95, column 2 at the first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made VHH antibodies with the anti-TAA specificities taught by Schlom.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a diagnostic agent such as taught by Hamers-Casterman with the specificity taught by Schlom in order to diagnose cancers such as taught by Schlom because Hamers-Casterman teach that the VHH antibodies could be an invaluable asset in the engineering of soluble VH domains for diagnostic, therapeutic and biochemical purposes.

20. Claims 22 , 33 and 35 are objected to because of the following informalities:

a. Claim 22 is objected to for reciting "devoid of CH1 domain" instead of "the CH1 domain."

b. Claim 33 is objected to for reciting "labelled" instead of "labeled."

c. Claim 35 is objected to for reciting "radio isotope" instead of "radioisotope."

Appropriate corrections are required.

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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